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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/522,912	01/28/2005	Ruediger Ridder	05033.0009.PCUS00	2061

27194 7590 03/23/2006

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EXAMINER	
PHAM, AUDREY S	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 03/23/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/522,912	RIDDER ET AL.	
	Examiner	Art Unit	
	Audrey S. Pham	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *1* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-42* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Re: Ridder, *et al.*
Claims 1-43 were pending.
Claim 43 was canceled.
Claims 1-42 are currently under consideration.

Election/Restrictions

Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions that are not so linked as to form a single general inventive concept under PCT Rule 13.1. In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

1. Claims 1-21, drawn to a method for discriminating metaplasias from neoplastic lesions in a biological sample in the course of cytological testing procedures comprising determining cells overexpressing at least one different INK4a gene wherein one different INK4a gene-product is a polypeptide.

2. Claims 1-21, drawn to a method for discrimination of metaplasias from neoplastic lesions in biological samples in the course of cytological testing procedures comprising determining cells overexpressing at least one INK4a gene wherein one different INK4a gene-product is a RNA molecule.

3. Claims 22-24, drawn to a kit comprising at least one or more probes for the detection of the overexpression of two or more INK4a gene-products in a biological samples.

4. Claims 25-27, 35-37 drawn to an immunogenic peptide derived from a cell cycle regulatory protein encoded by an alternative reading frame of the INK4a gene products and to the pharmaceutical composition comprising said peptide.

5. Claims 28-33, drawn to a method of treating tumors comprising the steps of administering to a subject in need thereof a pharmaceutical composition comprising one or more immunogenic peptides derived from a cell cycle regulatory protein encoded by an alternative reading frame of the INK4a gene locus.

6. Claims 34-37 drawn to a binding agent directed against the immunogenic peptide and to a pharmaceutical composition comprising one or more peptides and one or more binding agents.

7. Claims 38-41, drawn to a method for detecting immunological entities specifically recognizing the immunogenic peptides, comprising obtaining a sample, contacting the sample with a binding agent and assessing the immunological entities in said sample.

8. Claim 42, drawn to a kit comprising one or more immunogenic peptides derived from a cell cycle regulatory protein encoded by an alternative reading frame of the INK4a gene locus or one or more binding agents directed against said immunogenic peptides.

Rule 13.1 of the Patent Cooperation Treaty (PCT) states that an international application should relate to only one invention or to a group of inventions if all inventions are so linked as to form a single inventive concept; *i.e.*, if there is unity of invention. According to Rule 13.2, unity of invention exists only when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding special technical features. The term "special technical features" is referred to as those technical features that define a contribution which each of the inventions, considered as a whole, makes over the prior art (Rule 13.2). The determination is made on the contents of the claims as interpreted in light of the description and

drawing (if any). If there is special technical feature and/or if multiple products, processes of manufacture or uses are claimed, the first invention of the category first mentioned in the claims of the application will be considered as the main invention in the claims, see PCT article 17(3) (a) and 1.476 (c), 37 C.F.R. 1.475(d).

The inventions listed as groups 1-8 do not relate to a single general inventive concept as required under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The technical feature linking groups 1-8 appears to be methods and kits for assessing the presence or absence or level of INK4a gene product for use in detection and treatment of tumors.

However, the technical feature linking groups 1-8 appears to have been taught by other(s). For example, Sidransky *et al.* (US Patent Number 5,856,094, January 1999) taught a method for detecting a cell proliferative disorder in a tissue (column 3, lines 19-21) or for monitoring the progression of cancer (column 22, lines 4-10) by identifying a nucleotide sequence of $p16^{INK4A}$ and $P15^{INK4A}$ (column 4, lines 12-13) that can be expressed in an altered manner as compared to the expression of a normal cell (column 15, lines 47-49).

The technical feature linking the inventions of groups 1-8 does NOT constitute a *special* technical feature as defined by PCT Rule 13.2 as it does not define a contribution over the prior art. Therefore, restriction for examination purpose is proper.

Species Election

One or more of the above invention groups each contains multiple generic claims that include a plurality of alternatively usable substances or members. These alternative limitations are independent or distinct inventions such that they do not share a common utility or share a substantial structural feature disclosed as being essential to that utility (*See In re Harnisch*, 631 F. 2d 716, 206 USPQ 300 (CCPA 1980) and MPEP § 803.02). Because they are not so closely

related, a search and examination of the entire claim cannot be made without undue burden. The members of the alternative groupings are described in the following:

Groups 1-3, 7 are generic to a plurality of disclosed patentably distinct species comprising the following **overexpressions**: *presence, absence, or level* (recited in Claims 1, 22, 24, 38). The above species represent separate and distinct conditions that differs in pathology, mechanisms and populations such that one species could not be interchanged with the other. As such, each species would require different searches and the consideration of different patentability issues.

Groups 1-3 are generic to a plurality of disclosed patentably distinct species comprising the following **INK4a gene-products**: *wherein at least one of the INK4a gene-product has a molecular weight between 13 and 19kDa* (Claim 2); $p^{16INK4a}$ (Claims 3, 23), *and* p^{14ARF} (Claim 4, 23). The above species represent separate and distinct products with different structures and functions such that one species could not be interchanged with the other. As such, each species would require different searches and the consideration of different patentability issues.

Groups 1-2 are generic to a plurality of disclosed patentably distinct species comprising the following **labels**: *radioisotope, bioluminescent compound, a chemiluminescent compound, a fluorescent compound, a metal chelate, or an enzyme* (recited in Claim 13). The above species represent separate and distinct labels with different structures and functions such that one species could not be interchanged with the other. As such, each species would require different searches and the consideration of different patentability issues.

Groups 1-2 are generic to a plurality of disclosed patentably distinct species comprising the following **probes and its respective techniques**: *polypeptide* (Claim 14), *nucleic acid and in situ hybridization* (Claims 14, 17-18), *nucleic acid and PCR* (Claims 14, 19-20), *nucleic acid and LCR* (Claims 14, 19-20), *and antibody directed against an INK4a encoded gene-product and immunocytochemical staining procedure* (Claims 14-16). The above species represent separate and distinct probes and respective techniques that differ at least in reagents and methodologies. As such, each species would require different searches and the consideration of different patentability issues.

Groups 3, 8 are generic to a plurality of disclosed patentably distinct species comprising the following **procedures or kits**: *research and diagnostic* (recited in Claims 22 and 42). The above species represent separate and distinct procedures or kits that differ at least in reagents, and population samples such that one species could not be interchanged with the other. As such, each species would require different searches and the consideration of different patentability issues.

Group 3, Claim 22 is generic to a plurality of disclosed patentably distinct species comprising the following **components in the kit**: *ap16INK4a sample for carrying out a positive control reaction, a p14ARF sample for carrying out a positive control reaction, reagents for detection of p16INK4a, reagents for detection of p14ARF, one or more samples of INK4a gene-products for carrying out positive control reactions, and one or more reagents for the detection of INK4a gene products* (all recited in Claim 24). The above species represent separate and distinct components that differ in structures and functions such that one species could not be interchanged with the other. As such, each species would require different searches and the consideration of different patentability issues.

Group 4 is generic to a plurality of disclosed patentably distinct species comprising the following **immunogenic peptides**: *a peptide from the amino acid sequence of the cell cycle regulatory protein, a HLA-A3 restricted nonamer peptide, an HLA-A2 restricted nonamer peptide, an HLA-A*0201 restricted nonamer peptide, or a 15-mer peptide* (recited in Claim 26). The above species represent separate and distinct peptides with different structure and function such that one species could not be interchanged with the other. As such, each species would require different searches and the consideration of different patentability issues.

NOTE: Upon election of a peptide listed above, applicant is required to elect one SEQ ID NO from those listed in SEQ ID NO: 1-23, recited in Claim 27, as each sequence represents a patentably distinct species. Applicant is reminded that any claims not reading on the elected sequence will be withdrawn as being drawn to a non-elected invention.

Group 5 is generic to a plurality of disclosed patentably distinct species comprising the following **tumors**: *benign tumors, malignant tumors, carcinomas, sarcomas, leukemias, lymphomas, and dysplasias* (recited in Claim 31), *cervical cancer, lung cancer, gastric cancer, and colon cancer* (recited in Claim 32). The above species represent separate and distinct conditions that differ in etiology, pathology, and mechanism such that one species could not be

interchanged with the other. As such, each species would require different searches and the consideration of different patentability issues.

Groups 4, 6 are generic to a plurality of disclosed patentably distinct species comprising the following **binding agents directed against immunogenic peptides**: *a monoclonal antibody, a mini-antibody, an antigen binding fragment, an antigen binding peptidomimetic molecule, a polyclonal antibody* (Claims 34-35). The above species represent separate and distinct peptides with different structure and function such that one species could not be interchanged with the other. As such, each species would require different searches and the consideration of different patentability issues.

Groups 5 are generic to a plurality of disclosed patentably distinct species comprising the following **treatments**: *curative* (Claim 29), *preventive immunotherapy* (Claim 29), *and vaccination therapy* (Claim 30). The above species represent separate and distinct treatments that target different population samples and use different methodologies such that one species could not be interchanged with the other. As such, each species would require different searches and the consideration of different patentability issues.

Groups 4, 6 are generic to a plurality of disclosed patentably distinct species comprising the following **additional peptides**: *$p16^{INK4a}$, HPV E6, HPV E7, HPV E2 HPV E4, HPV L1, HPV L2, p27, p21, p15, p19, p53, pRb, MDM2* (all recited in Claim 37). The above species represent separate and distinct peptides with different structure and function such that one species could not be interchanged with the other. As such, each species would require different searches and the consideration of different patentability issues.

Group 7 is generic to a plurality of disclosed patentably distinct species comprising the following **immunological entities**: *a binding agent directed against said immunological entities, a binding agent directed against complexes of the immunological entities together with the respective peptides, and at least one peptide* (recited in Claim 38). The above species represent separate and distinct immunological components that differ in structure and function such that one species could not be interchanged with the other. As such, each species would require different searches and the consideration of different patentability issues.

Group 7 is generic to a plurality of disclosed patentably distinct species comprising the following **purposes**: *monitoring in the course of a therapy using peptides according to claim 1, monitoring in the course of the application of a pharmaceutical composition according to claim 35, and monitoring in the course of a use according to any one of the claim 28* (recited in Claim 39). The above species represent separate and distinct conditions that differ in population samples such that one species could not be interchanged with the other. As such, each species would require different searches and the consideration of different patentability issues.

Groups 7, Claim 38 is generic to a plurality of disclosed patentably distinct species comprising the following **samples**: *secretions, smears, body fluids, serum, blood, plasma, urine, semen, stool, bile, sputum, biopsies, cell-and tissue-samples, resection samples of tumors, tissue samples prepared by endoscopic means and needle biopsies of organs* (recited in Claim 41). The above species represent separate and distinct samples that differ in etiology, pathology and mechanism such that one species could not be interchanged with the other. As such, each species would require different searches and the consideration of different patentability issues.

Upon election of any one group, Applicant is required under 35 U.S.C. 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable.

Applicant is advised that a reply to this requirement must include an identification of the species that is elected consonant with this requirement, and a listing of all claims readable thereon, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election. Applicant is reminded that any claims not reading on the elected species will be withdrawn as being drawn to a non-elected invention.

Upon the allowance of a generic claim, Applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

Should Applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the Examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

Rejoining Claims

The Examiner has required restriction between product and process claims. Where Applicant elects claim(s) directed to a product and the product claim(s) is/are subsequently found allowable, the withdrawn process claim(s) that depend(s) from or otherwise include all the limitations of the allowable product claim(s) will be rejoined in accordance with the provisions of MPEP § 821.04. Process claims that depend from or otherwise include all the limitations of the patentable product will be entered as a matter of right if an amendment is presented prior to a final rejection or allowance, whichever is earlier. Amendment submitted after final rejection is governed by 37 CFR 1.116; amendment submitted after allowance is governed by 37 CFR 1.312.

In the event of a rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claim(s) and process claim(s) may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the withdrawn process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.**

Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Inventorship Amendment

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

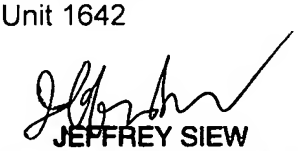
Contact Information

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Audrey S. Pham whose telephone number is (571) 272-3323. The Examiner can normally be reached during the hours of 8:30 AM - 5:30 PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Jeffrey Siew, can be reached during business hours at the telephone number: (571) 272-0787. The fax number for the organization, where this application or proceeding is assigned, is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Audrey S. Pham
Patent Examiner
Art Unit 1642



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SUPERVISORY PATENT EXAMINER